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TITLE: The Role of Cortical Plasticity in Recovery of Function Following Allogeneic Hand Transplantation

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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> In Year 1, we have obtained permissions for this work, completed piloting testing and collected data on several hand transplant and hand replant recipients as well as matched controls at multiple time points. Our preliminary findings indicate that: 1) Hand transplant recipients utilize the former cortical sensorimotor hand territory when using the affected hand. However, they continue to exhibit strong evidence for persistent, amputation-related, cortical reorganization. These persistent changes appear to diminish with recovery of hand function, suggesting that cortical reorganization is an important target for post-transplant rehabilitation.					
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## 1. Introduction

Hand transplant recipients provide a unique opportunity to investigate whether the central reorganizational changes that follow amputation are reversed when afferent and efferent signals between hand and brain are restored, and whether these changes are related to recovery of hand function. Our preliminary functional magnetic resonance imaging (fMRI) data suggest that areas of the sensory and motor cortex devoted to representing the hand prior to amputation come to represent the transplanted hand, even when received decades after amputation. We also find evidence that changes in cortical organization associated with unilateral hand amputation may not be fully reversed even a decade after transplantation; transplant recipients, like amputees, show increased activity in the former hand territory during movements of the adjacently represented face and of the intact hand. Importantly, the level of functional recovery appears to be associated with greater activity in the former hand territory when using the transplanted hand and with less evidence of persistent cortical reorganization. On the basis of our preliminary data, we hypothesize that experience-dependent central (brain) changes play a key role in the functional improvements known to continue throughout at least the first decade following hand transplantation, long after the expected completion of peripheral nerve regeneration. Developing a more complete understanding of the relationship between experience-dependent changes in brain organization and functional outcomes is critical to the long-term success of composite tissue transplantation. This project will yield new insights of fundamental relevance to improving the care and rehabilitation of transplant recipients, and broadly to other patients suffering from peripheral nerve or spinal cord injuries.

## 2. Keywords

Hand transplant, hand replant, amputation, brain reorganization, sensory, motor, hand function, recovery, functional magnetic resonance imaging

## 3. Accomplishments

### Major Goals Achieved: Year One

- Obtain IRB/HRPO approvals. We applied for and received permissions to conduct this research.
- Travel to Louisville for research meeting with collaborators to refine recruitment strategies and review all protocol details
- Refine devices and techniques used in protocols and conduct pilot tests:
  - Revised and tested somatosensory stimulation apparatus for face and hand during collection of whole-brain fMRI data.
  - Refined paired-pulse TMS techniques for evaluation of short-interval cortical excitation and inhibition.
- Recruiting, scheduling and testing patients and controls:
  - We obtained data from three hand replants, two hand transplants, one pre-transplant amputee as well as healthy controls.
- Preliminary data analysis
- Renewal of IRB/HRPO approvals

### Preliminary Data

#### *A. Mapping sensorimotor reorganization in the brains of hand transplant and hand replant recipients.*

*fMRI sensorimotor mapping protocol.* Participants were positioned supine in the scanner and moved different body parts according to auditory cues: “left hand”, “right hand”, “left foot”, “right foot”, or “lips”. Each cue was followed by a series of tones presented at a rate of 1 Hz, and participants were instructed to move the cued body part in pace with the onset of each tone. Movement blocks ended with the cue “stop”, and were 13s in duration, excluding movement instruction and stop cues. Each movement block was followed by 18s rest periods. Participants were asked to keep their eyes closed throughout.

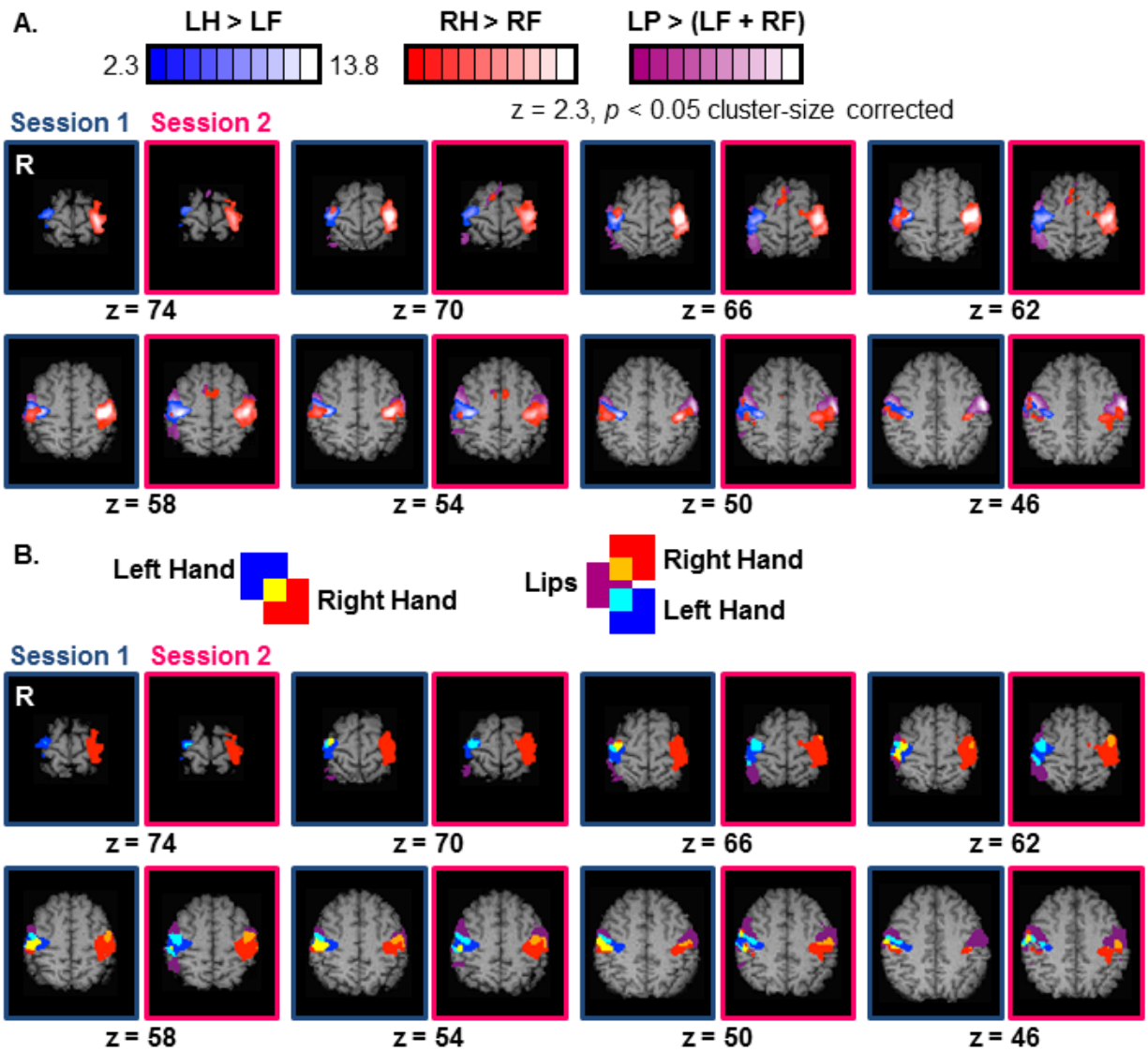
*Evidence for the reversal of amputation-related changes in cortical primary sensorimotor map organization.* DR is a right-hand dominant male who suffered traumatic amputation of his left hand proximal to the wrist at

the age 23 years. Thirteen years after amputation, patient DR underwent successful allogeneic hand transplantation. The data presented here were collected at 15 (Session 1) and 26 (Session 2) months post-transplant. During this interval of time, DR's hand function improved substantially. Carroll Test from 67 to 86; Dash test from 24.14 to 8.6.

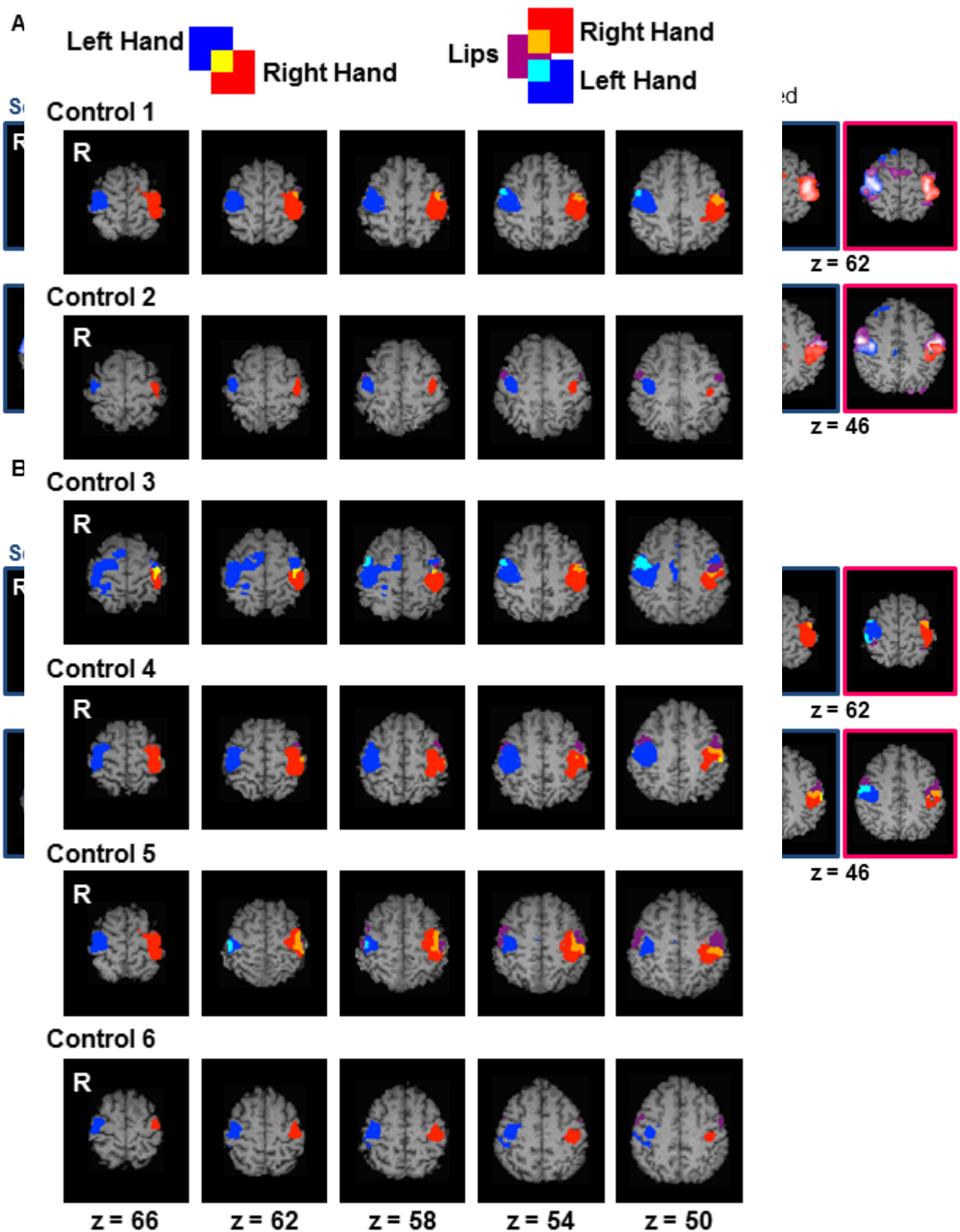
The fMRI results indicate marked reduction in the extent to which DR activates his ipsilateral sensorimotor cortex when moving his *non-transplanted hand* between testing session 1 & 2. This pattern reflects functional reorganization following the amputation that appear to persist even after the transplant (**Figure 1**). In patient DR, movements of his transplanted hand robustly activated contralateral sensorimotor cortex (SMC) and ipsilateral cerebellum, and the magnitude, location, and extent of this activity was remarkably consistent across Sessions 1 and 2. At 15 months post-transplant, movements of DR's non-transplanted hand also resulted in robust ipsilateral SMC activity, closely overlapping with preferential responses evoked by movements of his transplanted hand. *In other words, a considerable portion of DR's functionally-defined sensorimotor hand area contralateral to – and presumably devoted to the control of – his transplanted hand was also activated by movements of his non-transplanted hand.* Most exciting, the results from Session 2, at 26 months post-transplantation, reveal a striking reduction in the magnitude and extent of ipsilateral SMC activity during movements of DR's non-transplanted hand, and these changes are within the area of cortex preferentially responsive to movements of his transplanted hand. As this area of cortex continues to selectively respond to movements of DR's transplanted hand, paralleled by continuous improvements in sensory and motor function, response sensitivity to movements of the non-transplanted hand is reduced. As illustrated in **Figure 2**, these patterns differ from those exhibited by individual controls. **Further**, as is evident in Figure 3, we see very stable responses during hand movements in controls across two testing sessions, which suggests that the longitudinal changes in DR are valid and reliable markers of experience-dependent plasticity.

A second transplant – EH – also shows evidence of amputee-like bilateral SMC activity when moving his (left) non-transplanted hand. EH was tested 65 mths post transplant when his hand was functioning at a moderate level (Dash score = 53, Carroll score = 76). He was an amputee for 32 mths before receiving a transplant proximal to the wrist of his right dominant hand (**Figure 4**).

We find a different pattern in patient WH, who experienced an distal forearm amputation and immediate replantation. WH Following replantation of his amputated left hand, WH shows a different pattern than the transplant recipients. He exhibits very significant bilateral activation when moving either the affected or the unaffected hands (**Figure 5**).



**Figure 1. Patient DR: somatomotor map organization over time.** (A) Activity maps showing preferential responses for movements of the left hand (blue-to-white), right hand (red-to-white), and lips (purple-to-white) in patient DR at 15 (Session 1) and 26 (Session 1) months post-transplant. Axial slice images from Session 1 (blue outline) and Session 2 (pink outline) are shown side-by-side to facilitate comparisons. Set to the same thresholds, the maps indicate the statistical strengths of the effects for each of the three independent contrasts, as well as the locations of peak maxima. (B) The same activity maps shown in (A) masked as solid-colored-voxels to better illustrate the voxel-wise spatial extents and points of overlap between maps. Most notably, there is a striking reduction in the extent of activity preferentially responsive to movements of DR's right, non-transplanted hand within his right (ipsilateral) sensorimotor cortex from Sessions 1 to 2 (compare yellow-colored voxels, slices  $z = 58$  through 46). LH = left hand; RH = right hand; LP = lips; LF = left foot; RF = right foot.

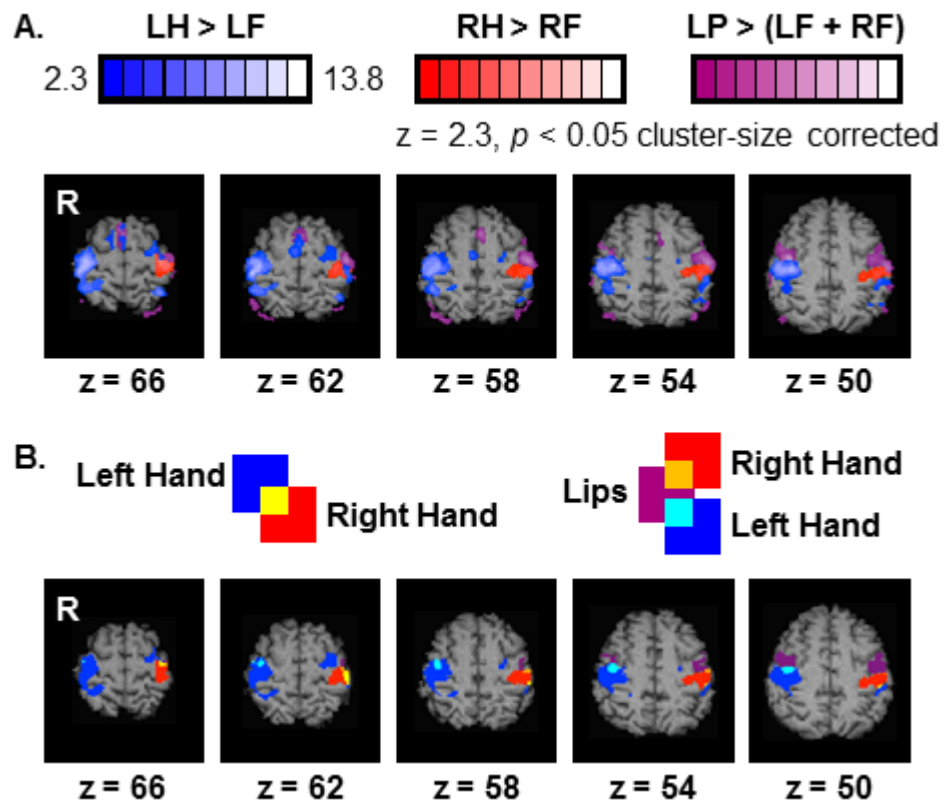


**Figure 2. Data from 6 healthy, age- gender- and handedness-matched controls.** Note the absence of areas exhibiting increased activity for movements of both hands.

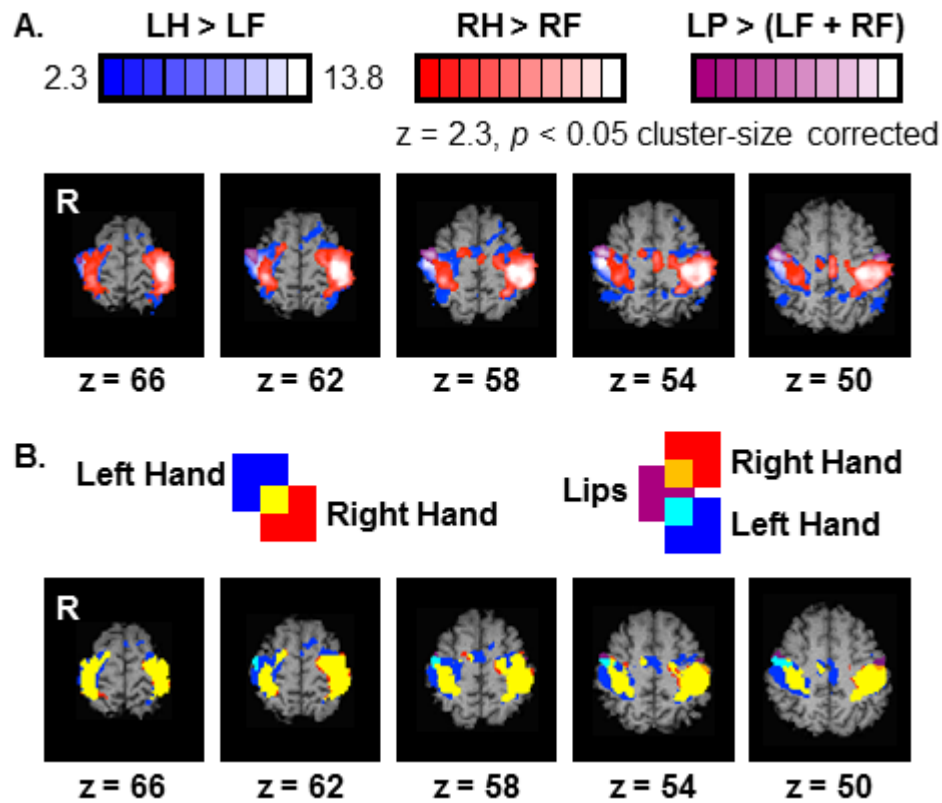
**Figure 3. Example Control participant (C1): somatomotor map organization over time.** Compare with Figure 1. A) Unlike patient DR, results from an age-, gender-, and handedness-matched healthy control participant show little evidence of ipsilateral sensorimotor cortex activity for movements of either hand, for either session. B) Specifically, in Session 1 only, a total of 58 voxels were activated within in left sensorimotor cortex for movements of the left (ipsilateral) hand. 37 of which overlapped with responses for movements of the

right (contralateral) hand (evident as yellow-colored voxels in slice  $z = 46$ ). LH = left hand; RH = right hand; LP = lips; LF = left foot; RF = right foot.

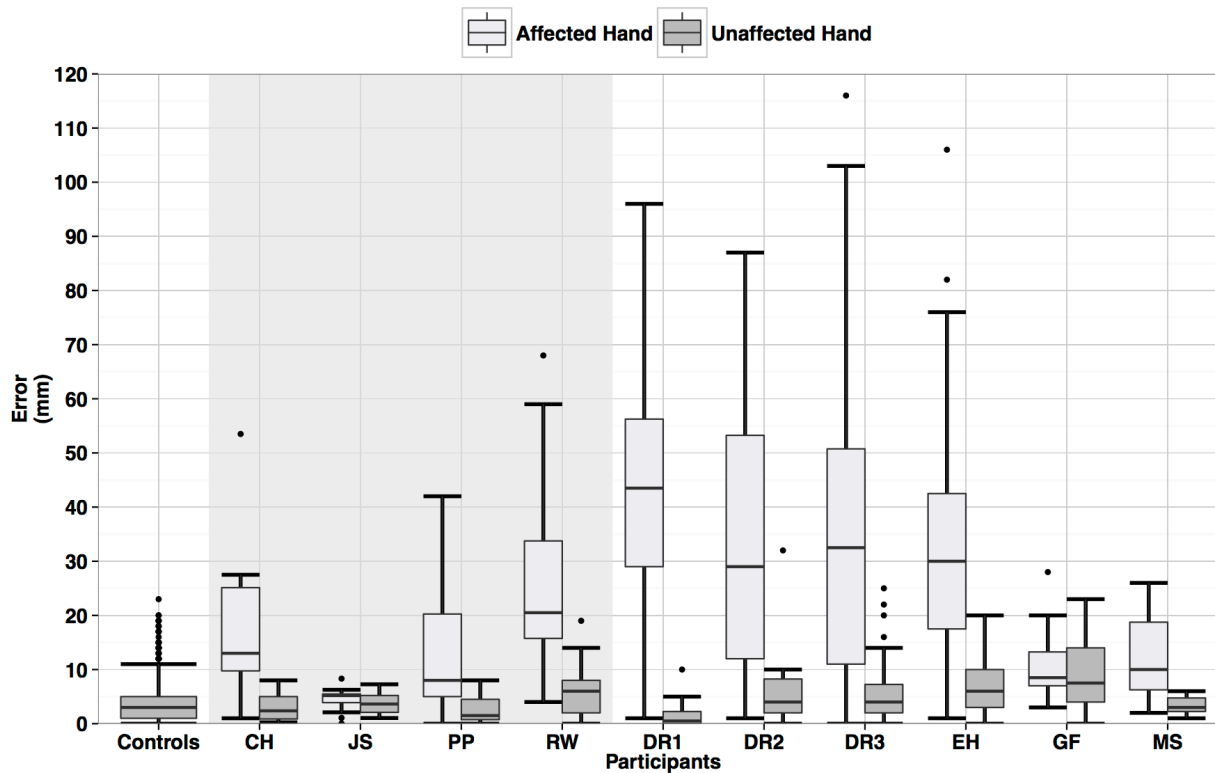




**Figure 4. Data from patient EH.** As for DR (Fig. 1), we see increased bilateral activity during movements of the intact hand.



*B. Sensory Functions.* **Figure 6** illustrates the accuracy with which our hand replant (gray shaded region) and hand transplant recipients are capable of localizing a light touch on the affected vs. unaffected hand. Note that DR has been evaluated on three different occasions. Overall, both groups exhibit lower mean error rates that are related to the time post-surgery. Transplant recipients on the far left show remarkably accurate recovery when tested 8 (GF) and 10 (MS) years post-transplant. This is consistent with evidence indicating continued gradual improvements in hand function long after the peripheral nervous system has completed reinnervation. We hypothesize that these changes are attributable to central (brain) adaptations.



**Figure 6.** The accuracy of touch localization without vision on the affected and unaffected hands. Hand replant recipients are displayed on the left against a gray background.

#### 4. Impact

It is too early to discern many of the broader impacts of this work. At this stage, we can say that the trainees involved in the project have benefited significantly in terms of their skills in this clinically-relevant area of research.

#### Training Opportunities

This project provided opportunities for postdoctoral and predoctoral trainees to gain additional experience in this area of research. They will be presenting aspects of this research at the Annual Meeting of the Society for Neuroscience in November, 2014.

As noted below, several presentations about this on-going project have been given to professional groups during this initial year.

#### 5. Challenges/Problems

- We experienced unanticipated artifacts in our electromyographic (EMG) recordings due to the delivery of transcranial magnetic stimuli (TMS, Aim 4). This required us to consult with other technicians and purchase a new set of amplifiers. We are working to get this system up and running with our protocol.
- We are experiencing some challenges scheduling several of the transplant recipients travels due to their work schedules.
  - We are investigating the possibility of conducting all portable aspects of the testing in Louisville during their required annual visits to the clinic there.
  - We have amended our IRB protocol to allow us to also recruit hand replant recipients through the Plastic Surgery Dept. at Southern Illinois University.

#### 6. Products

##### Book Chapter

**Frey, S.H.** (2014). *Why Brain Science is Essential to the Success of Hand Allotransplantation*. To appear in *The Science of Reconstructive Transplantation*. Gerard Brandacher (Ed.). Springer.

##### Presentations at Professional Conferences (\* Denotes invited address)

Valyear, K.F., Philip, B.A., Kaufman, C., Kutz, J., & **Frey, S.H.** How does the brain support the recovery of hand function for grasping following surgical hand replantation or transplantation? Am. Soc. Of Neurorehab. San Diego (Oct, 2013).

**\*Frey, S.H.** "The challenge of individual variability in rehabilitation neuroscience applications of fMRI. Am. Soc. Of Neurorehab. San Diego (Oct, 2013).

Baune N.A., Philip B.A., Kaufman C., Kutz J. & **Frey S.H.** (June 2014). Locognosia in hand replant/transplant recipients. Poster presented at the Advancing Neuroscience at MU Symposium, Columbia, MO.

Baune N.A., Philip B.A., Kaufman C., Kutz J. & **Frey S.H.** (November 2014). Improved sensation in a replanted or transplanted hand. Poster to be presented at the annual meeting of the American Society of Neurorehabilitation, Washington, D.C.

Baune N.A., Philip B.A., Kaufman C., Kutz J. & **Frey S.H.** (November 2014). Localization of touch on a replanted or transplanted hand: evidence for late improvements that may reflect central

adaptations. Poster to be presented at the annual meeting of the Society for Neuroscience, Washington, D.C.

Cirstea M.C., Peng H., & **Frey S.H.** (November 2014). Spectroscopic evidence for lower neuronal metabolism and time-dependent increases in inhibition within the former sensorimotor hand territory of chronic unilateral amputees. Poster to be presented at the annual meetings of the American Society of Neurorehabilitation and Society for Neuroscience, Washington, D.C.

Peng H., Cirstea M.C., Valyear K.F., & **Frey S.H.** (November 2014). Diffusion tensor tractography study of sensorimotor pathways in unilateral hand amputees. Poster to be presented at the annual meetings of the American Society of Neurorehabilitation and Society for Neuroscience, Washington, D.C..

Philip, B.A., & **Frey S.H.** (November 2014). Stability of precision drawing skills acquired with the non-dominant hand and associated changes in functional connectivity between sensorimotor hand representations. Poster presented at the annual meeting of the Society for Neuroscience, Washington D.C.

Philip, B.A., & **Frey S.H.** (November 2014). Skill acquisition with the non-dominant hand and associated changes in functional connectivity between sensorimotor hand representations. Poster presented at the annual meeting of the Society for Neurorehabilitation, Washington D.C.

Valyear, K.F., Philip, B.A., Kaufman, C., Kutz, J., & **Frey, S.H.** (June 2014). How does the brain support the recovery of hand function for grasping following surgical hand replantation or transplantation? Poster presented at the Advancing Neuroscience at MU Symposium, Columbia, MO.

Valyear, K.F., & **Frey, S.H.** (June 2014). The cortical bases of hand selection for object manipulation in humans: Insights from fMRI repetition suppression. Poster presented at the Advancing Neuroscience at MU Symposium, Columbia, MO.

Valyear, K.F., Philip, B.A., Kaufman, C., Kutz, J., & **Frey, S.H.** (November 2014). Amputation-related changes in inter-hemispheric interactions are reversible through transplantation of the human hand. Poster to be presented at the annual meeting of the Society for Neuroscience, Washington, DC.

## 7. Participants and Other Collaborating Institutions

### A. Participants

<b>Name</b>	<b>Benjamin Philip</b>
<b>Project role</b>	<b>Postdoctoral fellow</b>
<b>Nearest person month worked</b>	<b>6.0</b>
<b>Contribution to project</b>	<b>Data collection, analysis, reporting</b>
<b>Funding support</b>	<b>W81XWH-13-1-0496</b>

<b>Name</b>	<b>Kenneth Valyear</b>
<b>Project role</b>	<b>Postdoctoral fellow</b>
<b>Nearest person month worked</b>	<b>6.0</b>
<b>Contribution to project</b>	<b>Data collection, analysis, reporting</b>
<b>Funding support</b>	<b>W81XWH-13-1-0496</b>

<b>Name</b>	<b>Noah Marchal</b>
<b>Project role</b>	<b>Senior Research Technologist</b>
<b>Nearest person month worked</b>	<b>6.0</b>
<b>Contribution to project</b>	<b>Hardware &amp; Software Engineering</b>
<b>Funding support</b>	<b>W81XWH-13-1-0496</b>

<b>Name</b>	<b>Saadiya Aswad</b>
<b>Project role</b>	<b>Project Coordinator</b>
<b>Nearest person month worked</b>	<b>2.0</b>
<b>Contribution to project</b>	<b>Patient recruitment, scheduling, accounting</b>
<b>Funding support</b>	<b>W81XWH-13-1-0496</b>

<b>Name</b>	<b>Nathan Baune</b>
<b>Project role</b>	<b>Graduate Student</b>
<b>Nearest person month worked</b>	<b>2.0</b>
<b>Contribution to project</b>	<b>Patient testing, behavioral data analysis</b>
<b>Funding support</b>	<b>Departmental funding</b>

### B. Change in Other Support

Nothing to Report

### C. Collaborating Organizations

Christine M. Kleinert Institute

Louisville, KY

Patient identification, recruitment, behavioral evaluation, referral